

**Modulators of Receptors for Parathyroid Hormone
and Parathyroid Hormone-Related Protein**

Abstract

5 The present invention concerns therapeutic agents that modulate the activity of PTH and PTHrP. In accordance with the present invention, modulators of PTH and PTHrP comprise:

(a) a PTH/PTHrP modulating domain; and

(b) a vehicle, such as a polymer (e.g., PEG or dextran) or an Fc
10 domain, which is preferred;

wherein the vehicle is covalently attached to the C-terminus of the PTH/PTHrP modulating domain. The vehicle and the PTH/PTHrP modulating domain may be linked through the N- or C-terminus of the PTH/PTHrP modulating domain, as described further below. The

15 preferred vehicle is an Fc domain, and the preferred Fc domain is an IgG Fc domain. Preferred PTH/PTHrP modulating domains comprise the PTH and PTHrP-derived amino acid sequences described hereinafter. Other PTH/PTHrP modulating domains can be generated by phage display, RNA-peptide screening and the other techniques mentioned herein. Such
20 peptides typically will be modulators of both PTH activity and PTHrP activity, although such techniques can be used to generate peptide sequences that serve as selective modulators (e.g., agonists of PTH activity but not PTHrP activity).